Familial Pick's disease and dementia in frontal lobe degeneration of non-Alzheimer type are not variants of prion disease

The prion diseases are a group of neurodegenerative conditions affecting both humans and animals. They are transmissible after inoculation, have long incubation periods, and have been known as the spongiform encephalopathies, slow virus diseases, or transmissible spongiosis. The human diseases include Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), and kuru. All are associated with the deposition in the brain of an abnormal, partially protease resistant, isoform of normal, encoded protein, the prion protein (PrP). An impressive body of experimental evidence now argues persuasively that this abnormal isoform of PrP is the central and conceivably the sole component of the transmissible agent of these diseases. Human prion diseases have inherited, sporadic, and acquired forms and the inherited types are associated with coding mutations in the PrP gene. This availability of diagnostic genetic markers has enabled molecular diagnosis in patients not previously thought to be suffering from CJD or GSS and who carried clinical diagnoses including Alzheimer's disease, Pick's disease, and Huntington's disease. A wider phenotypic range of these disorders at the histological level has also been revealed after molecular diagnosis, with the identification of cases entirely lacking the usual pathological features of these conditions. This finding has led to a realisation that CJD and GSS are parts of a spectrum of what may be more appropriately designated prion diseases. The recent classification of fatal familial insomnian as an inherited prion disease further emphasises the need to search out their full phenotypic range. A similar, molecular reclassification is now beginning, based on the identification of mutations in the amyloid β protein in familial Alzheimer's disease and other familial neurological conditions such as hereditary cerebral haemorrhage with amyloidosis (Dutch type). For this reason we considered the hypothesis that both Pick's disease (PD) and dementia in frontal lobe degeneration of non-Alzheimer type (FLD) could be variants of prion disease. As with prion diseases, most cases occur sporadically but families showing an autosomal dominant pattern of inheritance are known. Pronounced frontal lobe features have been documented in at least one type of inherited prion disease; Pick type cells have been reported in CJD; spongiform change is seen in PD; and mutations in the PrP gene have been shown in both conditions. We therefore sought to examine the hypothesis that PD and FLD may be variants of prion disease by examining the PrP gene in the familial forms of these conditions for the presence of either known or novel mutations in the PrP gene and also by attempting to show the presence of the disease related isoform of PrP. We studied well characterised families with clinical conditions that met both classical clinical and histological criteria and in which the disease segregation shows an autosomal dominant pattern. All families have been documented previously.3–7 A Dutch family with PD one case presented with mental impairment at age 45, becoming apathetic and inactive. At age 48 she was completely dependent. Both the mother and two brothers had presented dementia. Postmortem examination of her mother had shown lobar atrophy and Pick bodies. The second Dutch family with PD was characterised by onset in their 40s of intractable disturbances and inactivity. There was confirmation of Pick's disease at necropsy. In a Swedish family with FLD 10 members in three generations were affected similarly with deterioration in personality and behaviour, lack of concern, and disinhibition. Later there were changes in speech with stereotyped phrases and echolalia. Three neuropathologically studied cases showed gross frontal atrophy with neuronal loss and gliosis of the superficial frontal cortical layers.

DNA was extracted from either blood or frozen brain tissue from an affected case from each family by standard techniques (using category 3 level microbiological containment to handle the brain tissue). The polymerase chain reaction (PCR) was used to amplify the PrP gene open reading frame and the PCR product was directly sequenced by the chain termination method.

Frozen brain tissue was only available (from two cases) from the FLD kindred. A 10% brain and a 5% spinal cord tissue sample histologically most affected area (frontal cortex) was prepared under microbiological containment level 3 conditions. Homogenate (4 μl) was spotted in duplicate on to nitrocellulose membranes and one filter of the pair was treated with proteinase K to digest the normal cellular isoform of PrP. The filters were then treated with the prion protein polyclonal antiserum to the 129 amino acid fragment (provided by D.J. Prusiner) and detection of bound primary antibody was with horseradish peroxidase conjugated goat antirabbit antiserum/enhanced chemiluminescence (Amersham). (KCL Sidle et al, in preparation). Each filter included both positive (histologically confirmed CJD) and negative controls (both histologically confirmed Alzheimer's disease and normal brain (provided by MRC Brain Bank, Institute of Psychiatry)).

With the exception of the known common polymorphic variation at codon 129 no mutation was identified in either allele in any of the families. Immunoblotting showed no evidence for the presence of the disease related isoform of PrP in the FLD cases studied.

These well documented cases of PD and FLD are not associated with PrP mutations. In the case at least of FLD no protease resistant PrP was detectable by immunoblotting. It seems likely therefore that PD and FLD, as described, are not variants of prion disease. It remains possible, however, that a proportion of less well defined cases and in particular those either without neuropathological confirmation or in which neuropathology is equivocal may turn out to be further examples of inherited prion diseases. Screening by PrP gene analysis and immunoblotting may be helpful diagnostically in these cases.
FVC and PEF plotted against time during the 24 hour period six days after the introduction of steroids. The time between the dotted lines represents a symptomatic decline in respiratory function.

ganglia noted on a scan 31 days after the onset of the illness, but normal scans were seen at day 45. In our similar case an MRI scan and a single photon emission computerised (SPECT) scan were normal.

A 22 year old woman presented with the acute onset of Sydenham's chorea. Three days before admission, she had noted paraesthesia of her left toe, and subsequently developed hemi-chorea of her left arm, face, and leg. Past history included mild asthma, atopic dermatitis, and mild iron deficiency anaemia as a result of menorrhagia. Medications included the oral contraceptive pill, inhaled bronchodilator, and an iron fotate preparation. Examination confirmed the left hemi-chorea and hemiballismus with choreic movement of the tongue and face. She had a sytolic murmur typical of mitral valve prolapse, but no signs of bacterial endocarditis.

Investigations included a normal full blood count, and her anti-nuclear antigen, β-human chorionic gonadotrophin, and thyroid function were negative or normal. A raised IgG cytomegalovirus antibody titre indicated past infection. The anti-DNase B titre was elevated but antistreptolysin O titre was normal. Brainstem auditory evoked responses, CT, MRI, and SPECT scan of her brain were normal. Serum copper estimation was slightly reduced at 0.6 μmol/l (NR, 12–22 μmol/l), and her antiecadiopil antiboddy was positive. An EEG showed an excess of theta transients in the right central and parietal head regions. A transoesophageal echocardiogram was diagnostic of rheumatic valvular disease, showing thickening of valve leaflets associated with mild stenosis (valve area, 2 cm²; gradient, 4–5 mmHg) and paravalvular leaks.

The left hemi-chorea persisted and oral tetrabenazine 25 mg twice daily was started with partial amelioration of the movement disorder. Penicillin 250 mg was started, and was, in fact, to continue until the age of 35 years. Advice was given about high dose antibiotic cover during dental or urogynaecological procedures.

The pathogenesis of Sydenham's chorea remains undefined. Its association with rheumatic heart disease was clarified in the mid-nineteenth century and the link between chorea and group A streptococcal pharyngeal infection was made 100 years later. Some anatomical studies of 106 patients who had Sydenham's chorea note perivascular infiltrates in the basal ganglia and this supports a presumed ischaemic process. Cerebral imaging studies of subjects with Sydenham's chorea have usually been normal. One report in this journal of a patient with ballismus who had a cerebral MRI scan performed 31 days after the onset of chorea showed high signal intensities throughout the basal ganglia on T2 weighted imaging. These changes were not present on repeat MRI scan, and the authors considered the appearance to be consistent with neither ischaemia nor demyelination.

Pharmacological studies suggest an abnormal regulation of striatal dopamine, and dopamine depleting agents such as tetrabenazine have been used therapeutically. Sera from patients with Sydenham's chorea showed heterogeneous antineuronal antibodies, but the precise nature of these antibodies and target antigens is unknown. SPECT imaging is a technique that allows analysis of brain perfusion using a radioactively labelled agent (exametazine), we scanned this patient's brain 10 days after the onset of chorea and showed a normal perfusion pattern. Together with a normal MRI 4 days after the onset of chorea, this case implies that there may be no acute perfusion abnormality in spite of post-mortem studies which often show basal ganglia vasculitis. This may either reflect the temporal profile of the condition or support the hypothesis that Sydenham's chorea is the result of an autoimmune process at the cellular level. Alternatively, the SPECT scanning technique may not be sufficiently sensitive to detect minor blood flow changes in deep cerebral structures.

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Paraneoplastic opsoclonus-myoclonus syndrome in metastatic ovarian carcinoma

Opsoclonus refers to involuntary, irregular, chaotic, conjugated eye movements in predominately horizontal directions with a frequency of 6–12/second. Characteristically, an accompanying intermittent myoclonus is lacking. An infrequent condition is encountered as opsoclonus-myoclonus syndrome (OMS) when opsoclonus is associated with focal or generalised myoclonus. Apart from rare causes such as vertebral ischaemia, haemorrhage of the pons or thalamus, hypersomnolent coma, head injury, or the combined administration of haloperidol and lithium, OMS has been reported in viral encephalitis or as a remote manifestation of neoplasms. Although in children, the major paraneoplastic cause of OMS is neuroblastoma, in adults, carcinomas of the oat-cell type of the lung, undifferentiated soft tissue, and thyroid malignancy are most frequently encountered. Recently, a young woman suffering from paraneoplastic OMS in Hodgkin's disease was reported in this journal. We describe OMS in the presence of metastatic epithelial ovarian cancer.

A 45 year old caucasian woman developed generalised shivers which severely interfered with walking two weeks before admission in November 1992. She also
Acute neuromuscular respiratory paralysis.

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